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The quest for evidence-based Ayurveda: lessons learned

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Ayurveda offers a unique opportunity to evolve a science of healthy, harmonious and long life. Its holistic approach to health and disease, involving body, mind and spirit, can provide a broader framework to understand research data emerging from reductionist biomedical sciences. This overview of a journey of a basic scientist into evidence-based Ayurveda suggests that a holistic gestalt and reductionist mechanisms are mutually complementary. However, such complementarity needs paradigm-shifting new research approaches. Over the past few decades, the outcome and unique lessons learned through network endeavours have given rise to integrative research programmes employing several trans-disciplines. Judicious applications have emerged: ethnopharmacology, botanical drug development, observational therapeutics, Ayurvedic pharmacoepidemiology, reverse pharmacology, Ayusoft, Ayugenomics, Rasayana, Systems Ayurveda and integrative medicine. Several hits, leads and ready-for-application products and processes have emerged. This article provides an account of the research journey, including some detours, towards the destination of several innovative projects, evidence-based Ayurveda and global acceptance of integrative medicine.

Keywords: Ayurveda, biomedicine, evidence-based protocols, holistic approach, reductionist mechanisms.

SCIENTIFIC research on Ayurveda has come a long way, especially over the last five decades. The earlier focus on isolating active ingredients from medicinal plants for drug development is now moving more towards scientific understanding of basic physiological concepts and processes outlined in Ayurveda. Pioneering work on chemistry and pharmacology of compounds derived from medicinal plants at premier institutes of CSIR, ICMR and DST under the composite drug research project gave many good leads like curcumin and products such as guglip[1]. At the outset, it is important to acknowledge pioneering contributions of many scientists and thinkers, including G. N. Sen, Ram Nath Chopra, Madan Mohan Malavia, K. N. Udupa, C. Dwarkanath, D. S. Antarkar, Sharadini Dahanukar, M. S. Valiathan, R. A. Mashelkar, G. V. Satyavati, B. M. Hegde, Ashok Vaidya, Sukh Dev, G. P. Talwar, C. K. Atal, B. N. Dhavan, Nitya Anand, S. S. Handa, Ranjit Roy Chaudhury, R. D. Lele, Krishna Kumar, R. H. Singh, Darshan Shankar, Gerry Bodeker, Alex Hankey, Vaidya Bhrihaspatidev Triguna, Vaidya P. S. Warrier and many others.

A fresh perspective on the scope of scientific research on the basic concepts of Ayurveda came from a decadal vision document highlighting the importance of Ayurvedic biology[2]. These views were also articulated at a symposium of the Indian National Science Academy (INSA), New Delhi followed by the 70th Annual Meeting of the Indian Academy of Sciences (IASc) at Varanasi in 2004. INSA and IASc have recognized the significance of India's traditional knowledge and the need to understand it more fully through modern science. These efforts led to significant funding from the Office of the Principal Scientific Advisor, Government of India, for the national research programme 'Science Initiatives in Ayurveda'. Still, scientific publications on Ayurveda in international peer reviewed journals have remained dismal[3].

India certainly needs to generate a sufficient evidence base for Ayurveda with the help of modern science and experimental rigour, in order for it to gain wider global acceptance[4]. Ayurveda and biomedical sciences share the same spirit of open and sincere scientific enquiry; yet their perspectives on the nature of man and the universe are different. Their basic philosophy, logic, ontology, epistemology and biomedical theories are distinct.

Ayurveda is basically pragmatic, systemic and holistic, whereas biomedical sciences are theory-based, structural and reductionist[5]. Biomedical science uses Aristotelian logic and reductionist scientific methodology to guide its propositions. Cellular and molecular biology governs its medical theories, whereas Ayurveda uses the Indian schemes of logic enshrined in the nyaya and vaishiseka schools, tridosha siddhant and dravya guna shastra to guide its medical theory. These epistemological differences call for due care and use of appropriate research methods when attempting the development of any evidence base.

A personalized, multi-factorial approach to healthcare and cure has been the basic strategy of Ayurveda as opposed to the generalized and single target strategy of biomedicine. Ayurveda considers body, mind and spirit along with their relationships with the bio-cultural environment. It is often argued that while Ayurveda receives

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acceptance and support from the general public, due appreciation from the scientific and medical community is not forthcoming[6]. Ayurveda includes knowledge about physiological, pathological and psychological aspects of botanical, zoological and mineral sources, along with detailed information about them. These bring distinct advantages to the natural product drug discovery process. Ayurvedic physicians and hospitals have long histories of drugs used-compositions, formulations and dosage regimens, therapeutic and untoward effects. These records are particularly valuable since effectively these medicines have been tested on people for thousands of years[7]. The rich knowledge resources and long experience of Ayurvedic therapeutics can pilot us to both future medicines and affordable healthcare. This article reviews a few important lessons and leads resulting from our research on evidence-based Ayurveda over the last three decades.

Lessons from tradition

While working with John Barnabas as a graduate student in biochemistry at the School for Biological Studies, Ahmednagar in 1980, I decided to work on Ayurvedic medicinal plants rather than choosing the more sought-after options in the field of protein biochemistry and evolutionary biology. Barnabas not only encouraged me to do so, but also provided the necessary facilities. I completed my dissertation on antimicrobial activity of *Semecarpus anacardium*, popularly known as Bhallataka, black nut or marking nut. This gave me an opportunity to work at different institutions in Pune, including the National Chemical Laboratory (NCL), Hindustan Antibiotics Ltd and Serum Institute of India, where special facilities for working with anaerobes were available. During this time I learned experimental microbiology besides my first exposure to natural product chemistry and the unique experience of working in a networked environment[8]. At the same time, a multi-institutional network project for development of an anticancer drug from *S. anacardium* was supported by the State Department of Science and Technology involving the Haffkine Institute, NCL, the Institute of Science, Mumbai and the Cancer Research Institute, Mumbai. I gained a research fellowship to continue for my PhD at the Haffkine Institute, which was a vibrant multidisciplinary biomedical institute where I learned anaerobic bacteriology[9], animal pharmacology, toxicology, immunology, and was exposed to the basics of pharmaceutical medicine and drug development[10].

Traditionally the nut shell oil of Bhallataka is supposed to have analgesic, anti-inflammatory, anti-microbial and anticancer activity. We planned several experiments to find evidence in support of these traditional claims. We studied animal pharmacology to support traditional claims and mechanisms of action for the anti-inflammatory and anti-arthritis properties[11]. Bhallataka oil showed significant anti-tumour activities in animal models of sarcoma and adenomas. There was statistically significant increase in lifespan in the treatment groups. Attempts were made to isolate the active principle using preparative HPLC coupled with anticancer activity testing of pure fractions; however, none of these was active. We could not identify any anticancer compound in pure form even after four years of intensive effort. The crude extracts and nut shell oil had significant anticancer activity, which was lost during the process of purification. These studies indicate the possibility of synergistic activities and the importance of processing and delivery of drugs.

Ayurveda contains information about how to take a particular drug both to enhance potency and reduce toxicity. This is called Anupana and calls for use of vehicles like honey, milk, warm water, etc. For example, Bhallataka is considered potentially toxic and needs to be processed and consumed along with suitable oil. In acute and subacute toxicity studies, fractions emulsified using Tween80 saline produced significant toxicity and 100% mortality at a dose of 25 mg/kg. Interestingly, the same dose in the same experimental conditions yielded zero mortality in a group that received fractions with peanut oil where signs of anabolic activity were observed, indicating a typical Rasayana effect. We also showed that traditional use involving peanut oil as a delivery vehicle was safe, while significant toxicity was observed at the same dose when the test material was converted into an emulsion[12].

Traditionally, Bhallataka is used as first aid for deep wounds due to thorns or nails, mainly to prevent pain and infection. This observation prompted us to study its activity on selected anaerobes responsible for infections in cases involving threat of tetanus or gangrene. In systematic activity directed fractionation, we were able to isolate three compounds known as monoene, diene and triene bhilawanols, which were shown to be responsible for specific anaerobic antibacterial activity against *Clostridium* spp.[13]. These observations offered unique learning and changed our attitude to traditional knowledge-inspired research. Ayurvedic pharmaceutics or Bhaishaja kalpana helped us understand the basis of various process and dosage forms like pills, decoctions, tinctures, wines, teas, linctus, syrups, creams and lotions, as described for the method of preparation, and their specific uses for various indications. A preliminary experiment noted that different Ayurvedic pills respond selectively and differently for parameters like dissolution and disintegration time. The results classified Ayurvedic pills into three distinct types resembling modern pharmaceutical dosage forms such as enteric-coated and slow-release types of tablet[14]. These studies taught us to respect traditional knowledge and the importance of selecting the correct experimental models and methodologies.

Interdisciplinary approach

In 1989, the University of Pune took a major decision to promote evidence-based research in Ayurveda. This was a forward-looking initiative that led to the establishment of the Interdisciplinary School of Ayurvedic Medicine (ISAM) under the Faculty of Science. I was invited to write a concept paper and then became the first Chairman of this novel School, supported by a strong advisory board consisting of eminent scientists from Ayurveda, natural, numerical, biomedical, social sciences and humanities disciplines. The University invited the eminent international Ayurveda scholar Subhash Ranade to be Professor in charge. In a period of three years, the School made significant progress by organizing national and international workshops on research methodology, and seminars on interdisciplinary research, collaborating with renowned institutions in India and abroad.

In 1993, P. V. Sukhatme was invited by the University of Pune as distinguished professor, giving me the opportunity to work with him and others, including Banu Coyajee, N. S. Deodhar, N. H. Antia, Rajnikant Arole and R. K. Mutatkar who recognized the value of establishing the Interdisciplinary School of Health Sciences (ISHS), converging modern concepts of public health with ancient systems of health, including Ayurveda and Yoga. Subsequently, ISAM was merged with ISHS and emerged as a pioneering University School addressing issues of 'health' and not limited only to 'medicine'. In 1994, the University Grants Commission recognized this School by approving a special grant for faculty positions, where I continued to work as professor. Today, ISHS remains one of the leading Schools, offering Master of Public Health and Master of Science programmes in health sciences, nutrition and dietetics as well as doctoral programmes in health biotechnology, genetics, Ayurveda and pharmacognosy. This led to significant contributions to ethnopharmacology, especially to inflammation and immunopharmacology, and some interesting research projects and publications on hypertension[15], obesity[16], anxiety[17], arthritis[18,19], inflammation[20,21], immunomodulators[22] and natural product drug discovery[23]. Thus traditional knowledge systems and ethnopharmacology proved useful in bioprospecting safer and effective medicines and treatments. During this period my research collaborations with Ashok and Rama Vaidya of Bharatiya Vidya Bhavan's Swami Prakashananda Ayurveda Research Centre were renewed. I had an opportunity to learn from others, including M. B. Bhide, Sharadini Dahanukar, S. M. Karandikar from K.E.M. Hospital and Research Centre in Mumbai.

Rasayana, immunomodulation and adjuvants

Rasayana tantra is one of the eight specialties of Ayurveda. It concerns rejuvenative recipes, dietary regimens, special health promoting behaviour and drugs. According to Ayurveda, when properly administered, Rasayana can bring many benefits: longevity, memory, intelligence, freedom from disease, feeling of youthfulness, excellence of luster, complexion and voice, optimum strength of physique and sense organs, respectability and brilliance. Various types of tissue-specific Rasayanas such as medhya, jeevaniya and lekhaniaya are mentioned in Ayurveda. Reviews of the current literature available on Rasayana indicate that immunomodulation is the most studied property/activity[24]. We have studied a few selected Rasayana plants, including *Withania somnifera* (Ashwagandha), *Asparagus racemosus* (Shatavari), *Tinospora cordifoloia* (Guduchi), *Phyllanthus embellica* (Amalaki) and *Semecarpus anacardium* (Bhallataka), and reported immunomodulatory activity for various standardized extracts and formulations prepared from them. We also evaluated their potential as antistress[25], anxiolytic[17], adaptogenic[26], immuno[27] and myeloprotectants[28]. In one particular study we reported Ashwagandha as a better and safer drug than Ginseng[29]. We also worked on anti-ageing activities of Ayurvedic medicines in topical application forms[30,31]. Such evidence base generating studies are important to properly position Ayurveda in the competitive international market.

Vaccine adjuvants

Newer vaccines like subunit and DNA vaccines are weakly immunogenic and require adjuvants. Ayurveda-based Rasayanas may offer better and safer immunodrugs that can be used as adjuvants in vaccines and cancer treatment[32]. We used a modified Kendrick test that involved challenge of live Pertussis cells intracerebrally where significant increase in antibody titre, reduced mortality and improvement in overall health was observed[33]. This observation has immense importance in the vaccine industry to obtain more efficient and sustained immunostimulation resulting in increased yield of immune sera and immunobiologicals[34]. These studies indicate applications of Rasayanas as potential immunoadjuvants that also offer direct therapeutic benefits resulting in lower morbidity and mortality[35]. Our group has successfully completed a DST project to develop a vaccine adjuvant in collaboration with our industry partner, Serum Institute of India. Four Indian patents have been filed in the area of vaccine adjuvant[36–38].

Cancer adjuvants

Most cancer chemotherapeutic agents are immunosuppressants and cytotoxic. We used cyclophosphamide induced immunosuppression to screen plant-derived drugs for anticancer and cytoprotective potential, and to demonstrate myelo and immuno-protective activity in

ascitic sarcoma-bearing animals[39]. We carried out activity-related extractions to identify best performing candidate drugs. One US patent has been filed in the area of cancer adjuvants[40]. This product will have significant importance in cancer therapeutics, especially to counter untoward effects of chemotherapy without compromising their anticancer activity[41].

Immunostasis activity

We studied pharmacodynamics of ashwagandha, shatavari and guduchi in experimentally induced tumours and infection mouse models, where one well-recognized cellular target for immunomodulation is Th1–Th2 balance[42]. We studied cytokine modulation *in vivo* using flow cytometry and showed that a 100 mg/kg dose resulted in a significant Th1 response (IL-2, IFN-g) in comparison to levamisole and cyclopsorin. In immune suppressed animals, ashwagandha exhibited significant dose-dependent potentiation of cellular and humoral immune response comparable to levamisole and faster recovery of CD4+ T cells percentages compared to control and cyclosporin[43]. The study indicated immunostasis activity and suggests its use where Th1–Th2 modulation is required.

Reverse pharmacology

Ayurveda knowledge allows drug researchers to start from time-tested and safe botanical material. The normal drug discovery course of 'laboratory to clinics' in this case actually becomes from 'clinics to laboratories' – a true 'reverse pharmacology' approach. In this process safety remains the most important starting point and efficacy becomes a matter of validation. The best example of bioprospecting using traditional knowledge is reserpine, the anti-hypertensive alkaloid from *Rauwolfia serpentina*, which became available as a result of work carried out by CIBA in India in close collaboration with Ayurveda experts. This process of natural product drug discovery was later named 'reverse pharmacology' by Ashok Vaidya[44,45]. A large number of molecules have come out of the Ayurvedic clinical base, including *Rauwolfia* alkaloids for hypertension, psoralens in vitiligo, *Holarrhena* alkaloids in amoebiasis, guggulsterones as hypolipidemic agents, piperidines as bioavailability enhancers, baccosides in mental retention, picrosides in hepatic protection, curcumines in inflammation and withanolides, and many other steroidal lactones and glycosides as immunomodulators. In the future, modern medicine could well come to be based on such ancient, Eastern, time-tested remedies, developed using advanced technologies from the West. In this process rationale and science will be key attributes. Traditional medicine-inspired drug discovery and development is therefore considered to be an efficient, faster and affordable strategy[46].

Multi-ingredient formulations

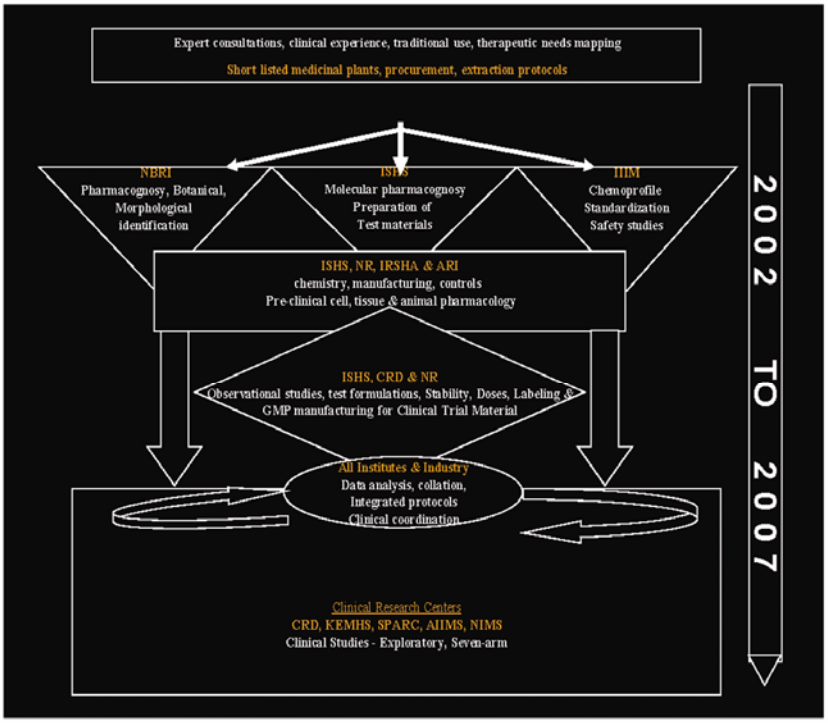
The Ayurvedic database gives information about botanicals that can best be used as single drugs in natural form or in processed form. It also gives a wide range of multi-ingredient combinations from simple mixtures to complex processed dosage forms. Modern medicine uses target-based single drugs, which have the distinct advantage of known pharmacokinetics, dynamics and precise dose-response relationships. However, recent trends indicate use of multi-drug therapy, particularly in the treatment of diseases like tuberculosis and HIV/AIDS. In these circumstances Ayurvedic multi-ingredient formulations offer distinct advantages, particularly in the area of difficult-to-treat chronic diseases such as diabetes, asthma, hypertension, cancer, arthritis and the like. Our work has helped establish the pharmaco-epidemiological evidence base through systematic documentation and analysis[47]. We have also addressed various aspects of quality control and regulatory issues relevant to botanical drugs[48].

The story of Artrex

The Ayurvedic formulary gives thousands of such multi-ingredient preparations and an excellent rationale for such formulations in the Ayurvedic classics. One such attempt to design a multi-ingredient formulation (Artrex) for the treatment of rheumatoid and osteoarthritis has been successfully completed and the formulation tested in a well-designed, randomized, double-blind, placebo-controlled clinical trial. This formulation gives therapeutic benefits in acute conditions of pain and inflammation, and it also addresses immunopathological interventions required for long-term management of slow, progressive, degenerative diseases like rheumatoid arthritis[49,50]. It has ingredients with analgesic and anti-inflammatory activities similar to NASAIDs and also includes ingredients with immunomodulatory, anabolic, disease-modifying and free-radical scavenging activities. Thus the formulation as a whole acts as a combination of NSAIDs and DMARDs[51]. The product was co-developed with BioVed Pharmaceuticals, and has been patented in India and in the US. It is available in the market in few countries[52].

Golden triangle initiative and NMITLI

A major thrust for scientific research on Ayurveda was given by R. A. Mashelkar through his Golden Triangle and New Millennium Indian Technology Leadership Initiative (NMITLI) which brought CSIR, ICMR and AYUSH institutions together to generate evidence-based Ayurveda. The Council for Scientific and Industrial Research (CSIR) supported an Ayurveda-based herbal drug development project under the NMITLI programme.


Expert consultations, clinical experience, traditional use, therapeutic needs mapping
Short listed medicinal plants, procurement, extraction protocols
NBRI
Pharmacognosy, Botanical, Morphological identification
ISHS
Molecular pharmacognosy Preparation of Test materials
IIIM
Chemoprofile Standardization Safety studies
ISHS, NR, IRSHA & ARI
chemistry, manufacturing, controls
Pre-clinical cell, tissue & animal pharmacology
ISHS, CRD & NR
Observational studies, test formulations, Stability, Doses, Labeling & GMP manufacturing for Clinical Trial Material
All Institutes & Industry
Data analysis, collation, Integrated protocols
Clinical coordination
Clinical Research Centers
CRD, KEMHS, SPARC, AIIMS, NIMS
Clinical Studies - Exploratory, Seven-arm
2002 TO 2007

Institutes
Interdisciplinary School of Health Sciences (ISHS), University of Pune
National Botanical Research Institute (NBRI), Lucknow
Indian Institute of Integrated Medicine (IIIM), Jammu (Formerly RRL-J)
Interactive Research School for Health Affairs (IRSHA), Bharati Vidyapeeth University, Pune
Agharkar Research Institute (ARI), Pune
Center for Rheumatic Diseases (CRD), Pune
Medical Research Center, Kasturba Society (MRC), Mumbai (Formerly SPARC)
All India Institute of Medical Sciences (AIIMS), New Delhi
King Edward Hospital & Research Center (KEMRC), Mumbai
Nizam Institute of Medical Sciences (NIMS), Hyderabad
Natural Remedies (NR), Bangalore
Zandu Pharmaceutical Works (ZPW), Mumbai; Arya Vaidya Pharmacy (AVP), Coimbatore; Arya Vaidya Shala (AVS), Kottakal; Dabur India Ltd (DIL), New Delhi; Nicolas Piramal India Ltd. (NIPL), Mumbai
Time: Five years

Figure 1. CSIR NMITLI arthritis project task and team.

Three projects were supported for Ayurveda-based herbal drug development for hepatitis, diabetes and arthritis. Following several rounds of national-level consultation involving Ayurvedic scholars, many drugs were short-listed. They entered a parallel track of open-label observational studies by selected Vaidyas and animal pharmacology studies for safety and efficacy.

Botanical drug development

The NMITLI project brought together experts, institutions of excellence and industries representing Ayurveda, modern science and modern medicine (Figure 1). The project also developed integrative protocols and appropriate research methodologies for evidence-based Ayurveda and botanical drug development[53]. This led to two platforms of drug formulations for treatment of osteoarthritis and rheumatoid arthritis. Based on preliminary studies, five formulations were selected for a randomized, placebo-controlled, seven-arm, multi-centric clinical trial with glucosamine as the positive control. Two formulations which performed statistically better than placebo and glucosamine were then taken up for mechanistic studies[54]. All the formulations prepared for clinical trials were manufactured and labelled generally in accordance with US FDA Guidance to Industry for botanical drugs. Most of the required tests were performed during the entire process starting from passport data of raw material, botanical identification, chemical profile and DNA analysis, and stability of the finished products[55–59]. *In vitro* studies using suitable cell and tissue culture models on these formulations revealed

significant chondroprotection (proteoglycan release, nitric oxide release, aggrecan release and hyaluronidase inhibition as markers) in an explant model of OA cartilage damage[60–63]. Safety and pharmacology studies of these formulations in animals demonstrated moderate analgesic and anti-inflammatory activities in both acute and chronic models. There was reasonable evidence for synergistic activity in the formulations compared to single drugs. The formulations were found to be safe according to OECD guidelines and were devoid of any significant genotoxicity or mutagenic activity in micronucleus tests. The bioprospecting of botanical materials, extractions, formulation development and manufacturing of the products was carefully done following WHO, US FDA and GMP guidelines. The drug master file and necessary documentation was maintained for review, records or regulatory needs and has been deposited with CSIR. An Indian and PCT Patent describing innovative process, formulation and use has recently been filed by CSIR[64].

Quality control

Quality and stability testing at pre-formulation stages is a crucial part of drug development. We studied physicochemical stability and biological activity of dried ashwagandha root aqueous extract under 6-month real-time and accelerated storage conditions. Characteristic constituents of ashwagandha root include withanolides such as withaferin A and withanolide A. We modified and validated the HPLC–DAD method for quantitative measurement of withanolides and fingerprint analysis[65]. The results suggest a significant decline in withaferin A and withanolide A content during real and accelerated conditions. HPLC fingerprint analysis showed significant changes in some peaks during real and accelerated storage. We also observed incidences of clump formation and moisture sensitivity under real-time and accelerated storage conditions. These changes were concurrent with significant decline in immunomodulatory activity during the third month of accelerated storage. Thus adequate control of temperature and humidity is important for WSE containing formulations. This study may help in proposing suitable guidance for storage conditions and shelf-life of ashwagandha formulations[66]. We carried out similar studies of chemical quality control of Ayurvedic botanicals, which may help in understanding stability of extracts and formulations[67,68].

Drug–herb interactions

Several diseases such as diabetes, hypertension and cancer may incur situations where modern drugs and botanical drugs are likely to be consumed concurrently. In such cases drug–herb interactions become important; yet very few studies are available in this field. We studied Guduchi extracts for possible interaction patterns with three conventional drugs used in the treatment of cancer, diabetes and arthritis. Acute as well as sub-chronic pretreatment with Guduchi does not have significant effect on cyclophosphamide pharmacokinetics. Guduchi also showed reversal of immune suppression associated with cyclophosphamide. Concurrent administration (acute as well as sub-chronic) of Guduchi with metformin showed beneficial pharmacokinetic as well as pharmacodynamic interaction leading to enhanced anti-hyperglycemic and antihyperlipidemic activity. Acute as well as sub-chronic pretreatment at therapeutic doses of Guduchi does not have significant effect on methotrexate pharmacokinetics. Therefore, Guduchi may be safe to take along with methotrexate[69].

We carried out pharmacokinetic and herb–drug interaction studies on rats fed with standardized traditional hydro-alcoholic extract and technology-based supercritical extract of *Cassia auriculata* for 12 weeks. Our studies indicate that both these extracts are pharmacologically safe and do not show any significant adverse reactions at the tested doses. The traditional hydro-alcoholic extract did not show any significant effect on pharmacokinetics; however, the technology-based super-critical extract caused a significant reduction in absorption of metformin. Our results indicate the need to include pharmacokinetic herb–drug interaction studies as an integral part of evidence for safety, especially for technology-based extracts[70]. We need several such studies on many commonly used synthetic drugs and botanical extracts, which may have the possibility of concurrent consumption.

Towards personalized medicine: AyuSoft and Ayugenomics

Ayurveda aims at holistic management of health and disease. It remains one of the most ancient medical systems widely practised in the Indian subcontinent and has a sound philosophical, experiential and experimental basis. It has close similarities with basic principles of traditional Chinese medicine[71]. The *Brihadatrayee* consisting of *Charaka*, *Sushruta* and *Vagbhata* are the main Ayurvedic classics, which describe some of its original and profound concepts. The most contemporary commentary on the *Brihadatrayee* is that of M.S. Valiathan in his Legacy series[72].

Ayurveda classifies the whole human population into three major constitutions, Kapha, Pitta and Vata; so their possible homologous relation to human genetic structure needs to be studied for validation. The Ayurveda database of human constitution, disease, detailed symptoms, logic of treatment and drug-activity libraries may provide new leads in individualized, standardized and uniform treatment, making medicine more a science and less an art to practice. Ayurveda is uniquely patient-oriented, where

the Ayurvedic physician diagnoses, treats and dispenses medicine to every individual patient. This important principle can form the basis for a form of personalized medicine which will give maximum therapeutic efficacy and high safety to a particular person with a particular disorder, under specified conditions depending on individual constitution and properties of materials. This specific prescription may also include supportive therapies, diet and lifestyle advice so as to regain physiological balance, finally resulting in removal of the disorder.

In anthropological terms, humans are classified into three major groups: Negroid, Mongoloid and Caucasoid, but genetically they are almost the same. Differences of colour, physique, behaviour and so on are due to single nucleotide polymorphism or SNPs. We have done SNP profiling across the intracellular folate metabolic pathway in healthy Indians[73]. We have studied genetic polymorphism of CYP2C19 in the Maharashtrian population[74]. We have also studied whether the thymidylate synthase and methylene tetrahydrofolate reductase genes are linked with methotrexate response[75].

Understanding and interpreting the importance of such individual variations in different populations for health and disease is an important basic principle of Ayurveda, and was underlined by Charaka several hundred years ago as 'Every individual is different from another and hence should be considered as a different entity. As many variations as there are in the universe, all are seen in human beings'[76]. At this point, the need to harmonize and organize the Ayurveda knowledge base in a retrievable software form arose. An informatics based decision support system with implications for personalized medicine based on the logic and essence of the *Brihadtrayee* and *Madhava Nidana* interpreted in terms of our ambitious project on Ayugenomics was conceived. The result was 'AyuSoft'.

AyuSoft

AyuSoft is a collaborative project between the Government of India's Centre for Development of Advanced Computing (C-DAC) and the University of Pune. While the Traditional Knowledge Digital Library (TKDL) helps in protecting intellectual property, AyuSoft converts the logic of classical Ayurvedic texts into comprehensive, authentic, intelligent and interactive knowledge repositories with the help of complex analytical tools (http://ayusoft.cdac.in). The AyuSoft database includes more than 5 lakh records, capturing information from nine texts, including the *Brihadtrayee* and *Madhava Nidana*. This knowledge base is accessible through a Decision Support System (DSS), data-mining tool and digitized searchable texts. The data-mining tool enables precise information searches using Boolean operators. Information related to diseases, causative factors, symptoms, treatment guidelines, drugs, dietary recipes, lifestyle changes and treatment procedures can be searched through complex queries employing any number of combinations of search strings. A search engine based on digitized Samhitas was developed as a part of AyuSoft. This facilitates the study of the Samhitas enabling quick reference searches and compilations to be made.

AyuGenomics®

In 2000, we proposed the original hypothesis that the concept of Prakriti in Ayurveda has strong genetic connotations. A pragmatic review highlighted how the practice of Ayurveda is personalized and can form the basis for pharmacogenomics and customized medicine[77]. The term Ayugenomics® was coined and proposed by me in 2002. In 2003, a first paper on the concept was published[78]. The term Ayugenomics® was legally protected by registering it as a Trade Mark with the statutory authorities of the Government of India[79]. Ayugenomics was planned as a platform to undertake the challenge of developing new strategies of drug discovery by integrating the ancient science and knowledge of Ayurveda with modern science, and the technologies of genomics, proteomics and pharmacogenetics. I presented the Ayugenomics concept to several scientists and venture capitalists for possible funding. Every time the question of proof of concept was rightly raised. Subsequently, Kalpana Joshi, Arvind Chopra and I decided to test the hypothesis using a cohort of rheumatoid arthritis patients available at the Centre for Rheumatic Diseases, Pune. The relationship of human leucocyte antigen (HLA) genes and RA is well known[80], so we used HLA DRB1 types to compare individuals with their Ayurvedic tridosha classification. We selected the HLA DRB1 gene because it has multiple alleles – many alternative forms of the gene. Our study showed a correlation between specific HLA alleles and Prakriti type, establishing a rationale and preliminary experimental support for the concept of an association between HLA alleles and the Ayurvedic tridosha theory of individual Prakriti types. This work led to a landmark publication establishing a genetic basis for the concept of Prakriti[81].

Although this was only a tiny hint at the concept of Prakriti, it set a valuable precedent, because a correlation is a very general, fundamental form of information – even graphs of algebraic relations in the physical sciences are only very high correlations between variables, when experimental errors are included. The implication of the existence of information in a scientific experiment is that there is some cause worth elucidating. Ayurveda points to the cause of the 'information' found in this experiment as being the more general concept of Prakriti. It justified further experiments on the Prakriti concept. Classifying humans based on phenotypes offers a challenge to biomedical science with the technology to look for underlying genetic variations among phenotypic datasets[82]. Descrip-

tions in Ayurveda indicate that individuals with Pitta Prakriti are fast metabolizers, whereas those of Kapha Prakriti are slow metabolizers. We hypothesized that different Prakritis may possess different drug metabolism rates associated with drug metabolizing enzyme polymorphism. We performed CYP2C19 genotyping in 132 unrelated healthy subjects of either sex by the polymerase chain reaction-restriction fragment length polymorphism technique, thereby observing significant correlations between CYP2C19 genotypes and major classes of Prakriti types[83].

Our preliminary studies thus demonstrated a probable genomic basis for metabolic differences attributable to Prakriti, possibly providing a new approach to pharmacogenomics. These results needed to be validated using genome wide association studies on larger and diverse sample size. In 2006, I was invited to start a project on 'Genomic variation analysis and gene expression profiling of human dosha prakriti based on principles of Ayurveda'. This project is supported by the Principal Scientific Advisor Office of the Government of India and involves a collaborative partnership between the Indian Institute of Science, Bangalore; the Centre for Cellular and Molecular Biology, Hyderabad, the Institute of Ayurveda and Integrative Medicine (Foundation for Revitalization of Local Health Tradition (FRLHT)), Bangalore; Manipal University, and ISHS at the University of Pune. This ambitious programme involves studies related to gene expression profiling, SNP-based genotyping, data validation by DNA sequencing, STR-based genotyping and gene polymorphism in *P450*, *MDR*, *GST*, *NAT* and *MCRs*.

The question of a genetic basis for traditional medicine is of interest, particularly to Indian, Chinese, Korean and other scientists, where approaches similar to Prakriti are part of the therapeutics. Our group's pioneering works have thus had a catalytic influence and several groups in India and abroad have undertaken research projects in areas related to Ayugenomics[84]. Several good papers have been published, and many more will come in the near future. Thus the journey of Ayugenomics from a proof of concept paper published in *Journal of Alternative and Complementary Medicine* (*JACM)* in 2005 has now reached a higher level of scientific appreciation with papers appearing in *PNAS*[85] and other high-impact journals[86,87]. CSIR has recently established a new line of research named Ayurgenomics, which is an integrative approach of Ayurveda and genomics for the discovery of predictive markers for preventive and personalized medicine. It has been truly heartening to witness the rapid progress in high-quality research on the basic principles of Ayurveda initiated through the modest efforts of our group.

Systems Ayurveda

The foundations and logic of Ayurveda are mainly based on Sankhya and Vaisheshika philosophies. The manifested parts of matter are microcosm representing Purusha or the living and macrocosm representing Loka or the universe; both can be assessed by similar logic and methods. The main aims of Ayurveda are to promote health and longevity, and cure disease. They are achieved by attaining homeostasis of dosha, dhatu, mala and agni. Appropriate conduct, including individualized lifestyle and diet helps restore health. Effects of dravya as diet or drug also as causative factor depend on properties and activities relative to the context. Processing (samskara) augments health-promoting properties of medicines, and reduces their toxicity. Disease processes are initiated by causative factors (hetu), and any disturbances in tissues or organs. Etiological processes, Samprapti, involve six steps (shatkriyakal) which manifest into disease. The holistic approach of Ayurveda management aims to establish health through multifarious treatment modalities, including counselling, avoiding causes, panchakarma, medicines, diet and surgical procedures.

The 'Systems Ayurveda' graphic notation describes schema of the Ayurveda knowledge base in a logic chart as entity relationships with its notation based on the Systems Biology Graphical Notation (SBGN) concept[88]. We have published the first poster of a proposed series broadly describing the logical flow, forward and backward loops, entity relations and their applications to health and disease. The 'whole to part' relation of Ayurveda philosophy is important for better understanding its comprehensive structure. The immense data include almost 300 variables describing the logical flow of concepts of Ayurveda which are presented using the SBGN approach for processes, entity relationships and activity flow (Figure 2).

Vaidya scientists

The interface between Ayurveda shastra and biomedical sciences is necessary for a creative dialogue between medical professionals from different systems of medicine. Today, many if not most Ayurveda students lack a robust functional theoretical foundation in either. There is a lack of exposure to contemporary advances and to disciplines like public health, cell biology, epidemiology, biomedical engineering, pharmaceutics, clinical pharmacology, immunology and pharmacogenomics, amongst others. To address these issues we have initiated an ambitious fellow programme 'Vaidya-scientists' to create a scholarly group of change agents, who are well versed in the richness of the Ayurveda classics and the details and insights of modern biology[89,90].

Ayurveda and integrative medicine

Historically Ayurveda has been progressive, dynamic and inclusive, building on great scientific, logical and

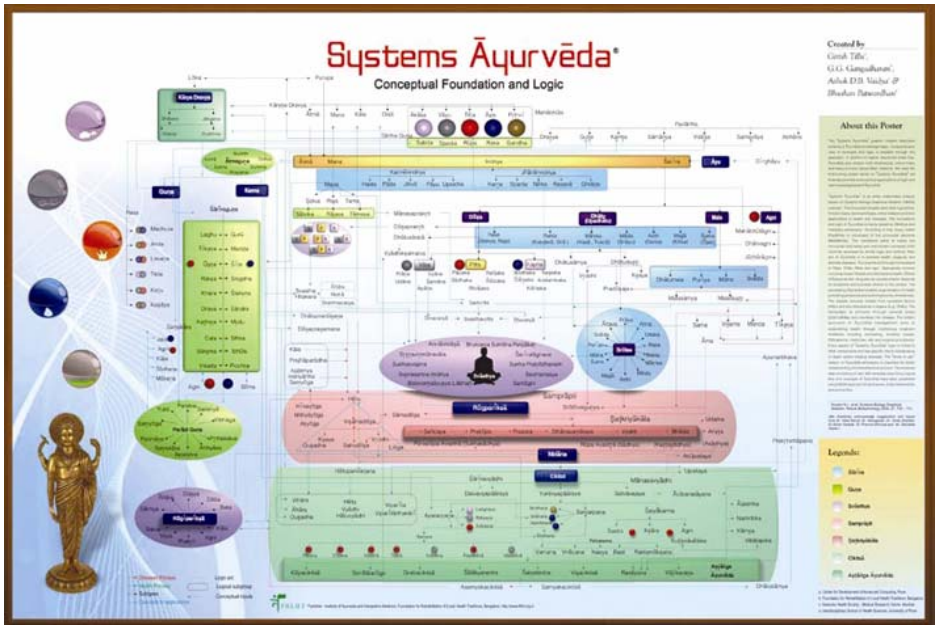


Figure 2. Systems Ayurveda.

Figure 3. Evidence-based Ayurveda: rationale of integrative study protocols.

philosophical foundations, but today it is in need of a renaissance to resuscitate its historic expansion and research orientation. To develop and practice the right model of integrative medicine for India, the Institute of Ayurveda and Integrative Medicine (www.iaim.edu.in) was established in 2010. This was a result of over 18

Box 1. Lessons learned.

- Ayurveda is not just a herbal medicine, but a science of life with a holistic approach to health and personalized medicine.
- Epistemological differences between Ayurveda and biomedicine should be taken into account when designing evidence-based research protocols.
- The classical approach of Ayurveda should not be compromised for convenience of existing scientific research methods.
- Appropriate research methodology and research protocols should be carefully designed, involving experts from Ayurveda and biomedicine.
- The holistic, integrative and systems approach of Ayurveda involving body, mind, and spirit is important, as is also the rigour of biomedical reductionist research to understand underlying structures, processes and mechanisms.
- Ayurvedic knowledge, logic, materials, processes, dosage forms, diagnosis, diet, therapeutics and personalized approach should be understood and valued during any preclinical and clinical studies.
- Basic concepts of Ayurveda such as Prakriti, Agni, Dhatus, Srotas, Rasayana and Shatkriyakal may provide new leads for biomedical research.

years of rigorous work at FRLHT at Bangalore founded by Darshan Shankar and Sam Pitroda. Subsequently, the *Journal of Ayurveda and Integrative Medicine* (www.jaim.in) was started. A new 100-bed, modern hospital is led by eminent vaidya Gangadharan, where integrative protocols for over 30 diseases have been developed and practised. This integrative hospital offers classical Ayurveda treatment along with close monitoring of patients before, during and after the treatment with the help of modern diagnostics. This approach draws the best from both the systems without compromising the principles of either. These initiatives primarily aim to recognize the importance of conserving and revitalizing the Ayurvedic and traditional knowledge systems using an integrative approach to explore mutual relationships with basic sciences, biomedicine and other contemporary health sciences[91]. The true success and test of the new, integrative approach will lie in its ability to recognize, respect and maintain the respective identities, philosophies, foundations, methodologies and strengths of all systems. Such an integrative exercise is extremely complex and a challenging balancing act-like riding a tiger[92].

Conclusion

Absence of evidence is not evidence of absence. While it is important to study the evidence base for Ayurveda, it is equally important to ensure that the epistemological differences between the two systems are taken into account when developing appropriate study protocols (Figure 3). We have learned many lessons over a period of time, which are important for future research on evidence-based Ayurveda (Box 1). We do hope that whenever questions about the scientific validity of Ayurveda are raised in India or abroad, such data will help gain wider acceptance for Ayurvedic medicines[93]. The knowledge base of Ayurveda, ranging from medicinal plants to personalized therapeutics, and scientific advances in biomedicine together can help in improving our understanding of health and disease processes. Such integrative approaches will facilitate the present quest for evidence-based Ayurveda for affordable and safe healthcare.

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